



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,042	10/25/2000	Shiyu Li	44908-00005	4438

7590 10/01/2002

Alan R Thiele  
Jenkins & Gilchrist, P.C.  
1445 Ross Avenue, Suite 3200  
Dallas, TX 75202-2799

EXAMINER

HOAS, WENDY C

ART UNIT PAPER NUMBER

1661

DATE MAILED: 10/01/2002

7

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/696,042

Applicant(s)

Li

Examiner

Wendy Couchoud Haas

Art Unit

1661



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 10/25/00
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-47 is/are pending in the application.
- 4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10/25/00 is/are a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5, 6 6) ☐ Other:

Art Unit: 1661

***Status of Application***

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1661.

***Drawings***

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

***Specification***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 1, 2, 14, 15, 27 and 28 are rejected** under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

Art Unit: 1661

and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

*Nature of the invention.* The claims are drawn to methods of increasing the production of camptothecins by a plant comprising the step of physically, biologically or ecologically controlling the amount of hormones produced by the plant.

*State of the prior art.* At the time the invention was made, it was known that removal of auxin from a plant would increase the production of camptothecin (CPT). This is taught by Vincent et al. [IDS reference C-49.] The effects of control of other hormones produced by the plant (i.e. ABA, cytokinins, ethylene, etc.) on camptothecin production were not known.

*Breadth of the claims.* The claims are drawn to controlling camptothecin production by controlling hormone amounts.

*Working examples.* A working example is included for auxin in the specification.

*Guidance in the specification.* The specification provides no specific guidance regarding the effects of controlling other hormones on CPT production.

*Predictability of the art.* The physiological art in general is acknowledged to be unpredictable. (MPEP 2164.03). In the instant application, applicants have disclosed a working method for controlling auxin levels only.

*Amount of experimentation necessary.* Further experimentation to determine which other hormone levels are affected by applicant's method and their particular effect on CPT production is needed.

Art Unit: 1661

For the reasons discussed above, it is clear that use of the claimed method for the control of hormone levels other than auxin in a plant *in order to influence CPT production* would require undue experimentation for one skilled in the art.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 1 through 47 are rejected** under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "camptothecins" in claims 1 through 47 is used by the claim to mean "camptothecin and its analogs and other indole and quinoline alkaloids," [Page 3, lines 6-8]. It is unclear whether a person of ordinary skill in the art would be able to determine the metes and bounds of the claimed invention from the terms indole and quinoline alkaloids, as these are somewhat general categories of chemicals. The number of chemical covered by the claim is too large for the claim to be distinct and the variation is too great to determine whether a particular indole or quinoline alkaloid should reasonably be considered to be covered by the claim.

**Claims 8, 21 and 34 are rejected** under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

Art Unit: 1661

applicant regards as the invention. Specifically, applicant states "heading back stems with a cut angle less than about 30 degrees to about 50 cm. from the ground", and "heading back stems with angles less than about 30 degrees from the vertical to about 50 cm. from the ground." First, it is unclear what a "cut angle" is. "Cut angle" is not a term of art. The Examiner notes that --crotch angle-- is a term of art, and is sometimes used to describe the angle between a trunk and a branch. Second, applicant appears to advocate cutting branches that come off of a main leader to the ground. This is impossible. Branches that come off a main leader can only be cut back to the point of origin. Correction and / or clarification regarding the intended meaning of these claims is needed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 1-3, 4-6, 27-29, 40-43, 46 and 47 are rejected** under 35 U.S.C. 102(b) as being clearly anticipated by Vincent et al. [IDS reference # C-49] taken in view of Li et al. [IDS reference # C-1] and Liu [IDS reference # C-34]. Vincent et al. teach a method for increased production of camptothecin from *Camptotheca acuminata* by pruning the auxin-producing shoot

Art Unit: 1661

tips and young leaves of 17 month old *C. acuminata* plants. This pruning process inherently decreases the amount of auxin produced by the plant until re-growth occurs. Applicant notes on page 15 of the specification that glandular (i.e. camptothecin-bearing) trichomes appear in greater densities on young leaves of a *C. acuminata* plant. Vincent et al. teach that their pruning method increases the amount of young vegetative tissues, and thus glandular trichomes on the plant. Vincent et al. also teach freeze-drying the harvested leaves of the pruned plants immediately after they the fresh weight is taken. The fresh weight is taken immediately after harvest. This freeze-drying of the fresh harvested leaves is known in the art to reduce the numbers of trichomes that fall away from the harvested leaves [see Li et al. which teach that camptothecin (CPT) is stored in the vacuoles of glandular trichomes and Liu, which teaches that tissues freeze-dried after harvest retain 27% more CPT.] Finally, Vincent et al. teach breaking the cell walls of the freeze-dried tissue mechanically and extracting the camptothecins from the tissue with a solvent.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1661

**Claims 1-6, 8, 10-12, 14-19, 21, 23-25, 27-32, 34 and 36-38 are rejected under 35**

U.S.C. 103(a) as being unpatentable over Vincent et al. in view of Li et al., Medic [IDS reference # C-53], McKey [IDS reference # C-117], Avery [in Cook, IDS reference # C-52], Bedker et al. [IDS reference # C-51], Purdue [IDS reference # C-44], Liu, Lopez-Myer et al. [IDS reference # C-36] and Bryant et al. [IDS reference # C-78]. The teachings of Vincent et al. are set forth above. Vincent et al. also teach the advantages of timing pruning at intervals of 6 weeks or greater; removal of apical dominance in order to facilitate increased biomass production; that the specific timing of pruning is important to the overall, long-term success of the camptothecin production cropping system; that is is most effective to leave some older leaf tissues on the plant in order to best induce young leaf production; and the advantages of a renewable leaf harvest system. Vincent et al. do not teach a method of pruning a plant during the first year using coppice (defined in the art as cutting a woody plant close to the ground), heading cuts, selective heading cuts and watersprout removal in order to increase the production of camptothecin. The terms coppice, heading cuts, selective heading cuts and watersprout removal are terms of art describing the specific type of pruning set forth in the claims and most specifically in claims 8, 21 and 34. Li et al. teach coppicing a *Camptotheca acuminata* plant during its first year (see, e.g. page 78, Figs. 29, 30), and Medic teaches pruning a woody plant using heading cuts, selective heading cuts, and removal of watersprouts.



Art Unit: 1661

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Liu et al. and Medic to prune a plant in order to increase the production of camptothecin by the plant.

Pruned trees produce more camptothecin. Li et al. teach that camptothecin is an alkaloid (pg. 10). McKey teaches that plants tend to respond to wounding by increasing alkaloid concentration in the wound area. Pruning a plant wounds it (see Medic). Therefore, pruning increases the amount of camptothecin produced by the plant.

Pruning a plant by applicant's method will create a bushy plant habit. Medic teaches that the purpose of heading and selective heading cuts, along with watersprout removal is to encourage growth lower on the plant, to make the plant full, and to encourage compact, bushy growth on shrubs. Avery (pg. 56-57) teaches that deciduous trees will resprout into a smaller, bushier form if they are coppiced. Bedker et al. teach that "given enough care and attention, plants can be pruned into nearly any form."

Creating a bushier plant habit creates more leaves. This is inherent, though the fuller growth is noted by Medic, Avery and Bedker et al., above. Li et al. teach that the leaves of *C. acuminata* have the highest concentration of camptothecin (CPT) of all the parts of the plant. Purdue teaches that the yield of leaves from *C. acuminata* tends to be very low. Pruning a plant to achieve a bushy habit is an obvious method to increase CPT production because it increases leaf number, and leaves have a greater concentration of CPT than other plant parts.

Art Unit: 1661

Creating a bushier plant habit also creates more young leaves. This is also inherent, because more sprouts and more leaves means more young leaves, particularly with repeated pruning and repeated regeneration. This fill-in effect of pruning is noted by Medic. In addition, Li et al. teach that the leaves of *C. acuminata* are short-lived. Therefore, regeneration of leaves is needed to sustain the plant. Finally, Liu and Lopez-Myer et al. teach that young leaves of *C. acuminata* have a higher concentration of camptothecin (CPT) than older leaves, and the highest concentration of CPT in the plant. Therefore, pruning a plant to create more young leaves is an obvious means of increasing the production of CPT.

Pruning also maintains a juvenile ontogenetic age in a plant. Bryant et al. teach that severe pruning of woody plants causes them to revert to a more juvenile form. Liu teaches that alkaloid concentrations in alkaloid-bearing plants are programmed to decrease as ontogenetic development proceeds. McKey's teachings reflect this decline by noting that alkaloids tend to appear earliest in the youngest, most actively growing tissues. Liu also notes this decline by teaching that leaves of the same age have varying CPT concentrations based on the age of the tissue they develop on, with leaves developing on younger tissues having higher concentrations of CPT. For these reasons, it would be obvious to prune a plant by applicant's method to increase CPT production because it creates more juvenile tissue and juvenile tissue creates more CPT, and also because it creates more young leaves (as noted above) on young tissue, and these young leaves growing on young tissues have a notably high CPT concentration.

Art Unit: 1661

The **motivations** for applicant to modify the system of Vincent et al. to incorporate the teaching of Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al. and Bryant et al. are numerous. Applicant would be **motivated** to produce a bushier plant habit in order to produce more leaves because leaves produce the most camptothecin (CPT) in the plant and the yield of leaves from *Camptotheca acuminata* is traditionally low. Applicant would be also be **motivated** to produce a bushier plant because bushier plants produce more young leaves. Young leaves produce more trichomes and thus produce more CPT. Applicant would also be **motivated** to prune the plant in order to maintain a younger ontogenetic age of plant tissues. Juvenile tissues produce higher concentrations of CPT. Applicant would also be **motivated** to optimize the timing of pruning based on the growth rate of the plant and the cultural conditions in the location the method is practiced in, especially by leaving some older leaf tissues on the plant and pruning no more often than once every six weeks, as suggested by Vincent et al., in order to maximize total CPT production and insure continued success of the planting. Thus, for all of the reasons listed above, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

**Claims 7, 20 and 33 are rejected** under 35 U.S.C. 103(a) as being unpatentable over Vincent et al. in view of Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al. and Bryant et al., as applied to **Claims 1-6, 8, 10-12, 14-19, 21, 23-25, 27-32, 34 and 36-38** above, and further in view of Cook [IDS reference # C-52] and Baldwin [IDS reference # C-73].

Art Unit: 1661

The teachings of Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al. and Bryant et al. are set forth above. Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al. and Bryant et al. do not teach pruning the plant's roots. Cook teaches that root pruning can be used to keep a shrub in its proper habit, "especially if judicious thinning and heading back of branches are done at the same time". Baldwin teaches that root stress strongly influences a plant's alkaloidal response to damage (showing that pot bound tobacco plants have no response to induced herbivory but plants with ample root room do respond).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al. and Bryant et al. in conjunction with the methods of Cook and Baldwin in order to induce a plant to produce more camptothecin for the reasons stated above. Applicant would be particularly **motivated** to do so because it would be desirable to maintain the advantageous shrub-like habit of the pruned plants. A further **motivation** comes from Baldwin's teaching which suggests that without root pruning, the method may cease to work once a critical mass of roots is reached. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

**Claims 13 and 26 are rejected** under 35 U.S.C. 103(a) as being unpatentable over Vincent et al. in view of Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer

Art Unit: 1661

et al. and Bryant et al., as applied to **Claims 1-6, 8, 10-12, 14-19, 21, 23-25, 27-32, 34 and 36-38** above and further in view of Baldwin and Baldwin (Oecologia) [IDS reference # C-69]. The teachings of Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al. and Bryant et al. are set forth above. Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al. and Bryant et al. do not teach pinching the leaf tip area of a portion of the leaves on the stem 6 to 8 days before harvest. Baldwin teaches that plant subjected to manual defoliation designed to mimic herbivory (i.e. partial leaf removal) undergo rapid increases in alkaloid production (between 438% and 5,319%) in 8 days. Baldwin (Oecologia) teaches that how a leaf is damaged is as important as the amount of damage. Leaves produce the greatest increase in secondary metabolites when the veins, interveinal tissues and midrib are all wounded when the leaf is partially pinched off.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al., Bryant et al., Baldwin and Baldwin (Oecologia) in order to induce a plant to produce more camptothecin (CPT). Applicant would be particularly **motivated** to use these methods because Baldwin and Baldwin (Oecologia) clearly show that partial leaf damage accross the tip will result in dramatically increased secondary metabolite production in 8 days or less. CPT is a secondary metabolite, therefore use of this method would dramatically increase CPT production. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Art Unit: 1661

**Claims 22 and 35 are rejected** under 35 U.S.C. 103(a) as being unpatentable over Vincent et al. in view of Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al., Bryant et al., Cook and Baldwin, as applied to **Claims 7, 20 and 33** and further in view of Baldwin (Oecologia). The teachings of Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al., Bryant et al., Cook and Baldwin are set forth above. Baldwin also teaches that plant subjected to manual defoliation designed to mimic herbivory (i.e. partial leaf removal) undergo rapid increases in alkaloid production (between 438% and 5,319%) in 8 days. Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al., Bryant et al., and Cook do not teach pinching the leaf tip area of a portion of the leaves on the stem 6 to 8 days before harvest. Baldwin (Oecologia) teaches that how a leaf is damaged is as important as the amount of damage. Leaves produce the greatest increase in secondary metabolites when the veins, interveinal tissues and midrib are all wounded when the leaf is partially pinched off.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Vincent et al., Li et al., Medic, McKey, Avery, Bedker et al., Purdue, Liu, Lopez-Myer et al., Bryant et al., Baldwin and Baldwin (Oecologia) in order to induce a plant to produce more camptothecin (CPT). Applicant would be particularly **motivated** to use these methods because Baldwin and Baldwin (Oecologia) clearly show that partial leaf damage accross the tip will result in dramatically increased secondary metabolite production in 8 days or less. CPT is a secondary metabolite, therefore use of this method would dramatically increase

Art Unit: 1661

CPT production. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

**Claims 43 and 44 are rejected** under 35 U.S.C. 103(a) as being unpatentable over Vincent et al. in view of van Hengel et al. The teachings of Vincent et al. are set forth above. Vincent et al. do not teach breaking trichome walls using ultrasound. Van Hengel et al. teach a method of breaking trichome walls of *Camptotheca acuminata* with ultrasound [sonification]. Van Hengel et al. also teach that their method recovered high yields of camptothecin, was faster than previously known methods and gives good results.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of van Hengel et al. to break trichome cell walls using ultrasound in order to increase the amount of camptothecin harvested from a plant. Van Hengel et al. provide a **motivation** for this combination by noting that their method is effective, fast and gives good results. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

**Claim 43 and 45 are rejected** under 35 U.S.C. 103(a) as being unpatentable over Vincent et al. in view of Gershenzon et al. The teachings of Vincent et al. are set forth above. Vincent et al. do not teach breaking trichome walls using a homogenizer. Gershenzon et al. teach a method of extracting the contents of glandular trichomes of peppermint with a cell

Art Unit: 1661

homogenizer. Gershenson et al. also teach that their method recovered high yields of glandular products from large amounts of plant material while minimizing contaminants, and that their method translates well to a wide variety of plant species.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Gershenson et al. to break trichome cell walls using a homogenizer in order to increase the amount of camptothecin harvested from a plant. Gershenson et al. provide a **motivation** for this combination by noting that their method is effective for recovering a high yield of products and is also easy to use. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.



Art Unit: 1661

*Future Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Wendy C. Haas whose telephone number is (703) 308-8898. The Examiner is normally available Monday through Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Bruce Campell, can be reached on (703) 308-4205. The fax number for the group is (703) 305-3041 or (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Matrix Customer Service Center whose telephone number is (703) 308-0196.

W.C. Haas

A handwritten signature in black ink, appearing to read "Bruce Campell", with a stylized, cursive script.

**BRUCE R. CAMPELL, PH.D  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600**